Doc Code: AP.PRE.REQ

PTO/SB/33 (07-05)
Approved for use through xx/xx/200x. OMB 0651-00xx
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) VASG-P01-002

	Application Number	Filed
	10/800,350	March 12, 2004
	First Named Inventor: Krasnoperov et al.	
	Art Unit: 1642	Examiner: S. E. Aeder

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 54,144
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

Signature

Z. Angela Guo, Ph.D.
Typed or printed name

(617) 951-7546
Telephone number

August 4, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: 8/4/2008 Signature: Debra M. Gilbride (Debra M. Gilbride)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: 8/4/2008 Signature: Debra M. Gilbride
(Debra M. Gilbride)

Docket No.: VASG-P01-002
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Krasnoperov et al.

Application No.: 10/800,350

Confirmation No.: 2293

Filed: March 12, 2004

Art Unit: 1642

For: POLYPEPTIDE COMPOUNDS FOR INHIBITING ANGIOGENESIS AND TUMOR GROWTH

Examiner: Sean E. Aeder

REMARKS ACCOMPANYING PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated February 5, 2008, Applicants respectfully request that a panel of examiners review the pending rejections. Applicants enclose the requisite Notice of Appeal, Pre-Appeal Brief Request for Review, a Petition for an extension of time, along with the remarks set forth below. Applicants respectfully request reconsideration in view of the following remarks.

REMARKS

Claims 26-29, 32-34, and 63-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stephenson et al. in view of Queen et al. Applicants respectfully traverse. Applicants maintain the arguments already made in the Response filed in November 13, 2007 and contend that the cited references do not render the claims obvious.

First of all, the alleged combination of Stephenson et al. and Queen et al. fails to teach all elements of the claims. Independent claim 26 is directed to an isolated monoclonal antibody which binds to an extracellular domain of an EphB4 protein and promotes apoptosis in a tumor cell, wherein the antibody is selected from bispecific, single-chain, chimeric, human, and humanized antibodies. Applicants emphasize that the claimed EphB4 antibody is clearly functionally defined by its ability to promote apoptosis in a tumor cell.

By contrast, Stephenson et al. disclose a polyclonal EphB4 antibody (H-200) purely for detecting expression levels of the EphB4 protein. Stephenson et al. do **not** teach or suggest a monoclonal EphB4 antibody which promotes apoptosis in a tumor cell. The other cited reference (Queen et al.) fails to bridge the gap between Stephenson et al. and the claimed invention. Accordingly, the alleged combination of Stephenson et al. and Queen et al. fails to teach all elements of the claims, such as a monoclonal antibody against EphB4 that promotes apoptosis in a tumor cell.

In the prior Office Action dated July 11, 2007, the Examiner asserted that "the claiming of the unknown property of inducing apoptosis, which is *inherently* present in the combined teachings of the prior art, does not make the pending claims patentable. In the absence of evidence to the contrary, the combined teaching of Stephenson et al and Queen would predictably produce the antibodies recited in the pending claims" (page 6, lines 18-22, emphasis added).

In the Response filed in November 13, 2007, Applicant provided arguments that the legal standard for inherent anticipation is not met in this case. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient'" (emphasis added). *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). This is a strict standard, which requires necessity. Probability, possibility, or even near certainty (*e.g.*, "almost always") would not satisfy the legal standard. *Id.*

In this case, the Examiner has not provided any legal or scientific basis that the antibodies disclosed in the cited reference are capable of promoting apoptosis in a tumor cell. In making the assertion, the Examiner seems to assume that all antibodies against EphB4 would promote apoptosis in a tumor cell. To the contrary, it is well known in the art that antibodies are unpredictable in nature. Indeed, the Board of Appeal noted that: "[h]ybridoma technology is an empirical art in which the routineer is unable to foresee **what particular antibodies** will be produced and which specific surface antigens will be recognized by them (emphasis added)." Ex parte Old, 299 U.S.P.Q. 196, 200 (PTO Bd. App. 1985). One of skill in the art would know that not all antibodies against EphB4 is capable of promoting apoptosis in a tumor cell. Applicants'

specification (e.g., pages 102-104 and Figure 59) substantiates the conclusion that hybridoma technology is an empirical art and a skilled artisan is unable to foresee what particular antibodies will be produced.

In response to Applicants' arguments, the Examiner asserts that "monoclonal antibodies that function as therapeutics to target EphB4 colon cancer cells taught by the combined teachings of Stephenson et al and Queen et al include monoclonal antibodies *comprising cytotoxic agents* that function as immunotoxins to kill target cells (see discussion of immunotoxins at lines 1-24 of column 35 of Queen et al, in particular) that would promote apoptosis" (Office Action, page 8, lines 8-14, emphasis added).

Applicants respectfully submit that the Examiner has misconstrued the claimed invention. Independent claim 26 clearly specifies that the EphB4 monoclonal antibody, which does not comprise any cytoxic agents, is capable of promoting apoptosis in a tumor cell. The Examiner fails to appreciate that the apoptosis-promoting activity is a functional feature of the claimed monoclonal antibody *per se*. In another word, the claimed antibody does not need to comprise any cytotoxic agents in order to have the apoptosis-promoting activity. By contrast, the cited prior art describes that an EphB4 antibody can promote apoptosis only when it comprises cytoxic agents. A skilled artisan would know that the apoptosis-promoting activity disclosed in the cited prior art results from the cytoxic agents, rather than the EphB4 antibody. Accordingly, the alleged combination of Stephenson et al. and Queen et al. fails to teach the antibody as recited in claim 26.

In addition, Applicants submit that the Examiner has not satisfied the requirement of establishing a *prima facie* case of obviousness against independent claim 26. According to the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register Vol. 72, No. 195 at pages 57,526-57,535) (effective October 10, 2007) ("the Guidelines"), a § 103 claim rejection based on a purported teaching, suggestion or motivation to combine prior art references to arrive at the claimed invention must support a conclusion of obviousness by including: (1) a finding that there was some teaching, suggestion or motivation to modify or combine the cited references; (2) a finding that there was a reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary in view of the specific facts.

Applicants submit that a skilled artisan would not have had a reasonable expectation of success even if these references were combined, given the state of the art at the time of the invention. As described above,

it was well known that antibodies are unpredictable in nature and a skilled artisan is unable to foresee what particular antibodies will be produced (see, e.g., Ex parte Old, supra). In view of the unpredictable nature of antibodies, the lack of evidence that EphB4 antibodies could promote apoptosis, and the lack of guidance on how to make and select EphB4 antibodies with a particular feature (e.g., apoptosis-promoting activity), a skilled artisan could not predict that apoptosis-promoting EphB4 antibodies would be successfully made.

Moreover, there is no suggestion or motivation for a skilled artisan to make apoptosis-promoting EphB4 monoclonal antibodies as recited in claim 26. Stephenson et al. disclose a polyclonal EphB4 antibody (H-200) purely for detecting expression levels of the EphB4 protein. Although Stephenson et al. speculate that "Eph-ephrin signalling may be important in the progression of colon cancer and that therapies that target this receptor may find application in anti-cancer systems" (page 2, left column), Stephenson et al. **fail** to suggest or teach use of any antibodies as therapies, let alone any EphB4 monoclonal antibody which is capable of promoting apoptosis. Rather, Stephenson et al. describe developing agents for reducing EphB4 **expression** for therapeutic purposes (page 7, left column, under "Conclusions"), thus teaching away from the claimed invention directed to antibodies. Even if a skilled artisan would have been motivated to make EphB4 antibodies as therapeutics, there is no reasonable expectation of success in making the claimed apoptosis-promoting antibodies for the reasons as described above. Although Queen et al. disclose methods for producing humanized immunoglobulins, antibody fragments, bifunctional antibodies, Queen et al. fail to cure the deficiencies of Stephenson et al.

In view of the above, Applicants submit that all of the pending claims are non-obvious over Stephenson et al. in view of Queen et al. Even if the cited references were combined, the combination still fails to teach each and every limitation of the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

Claims 26-29, 32-34, and 63-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Inada et al., in view of Stephenson et al., and in further view of Queen et al. Applicants respectfully traverse these rejections.

Applicants reiterate the arguments already made above for rebutting the obviousness rejection over Stephenson et al. Like Stephenson et al., Inada et al. do not suggest or teach any therapeutic use of an EphB4 antibody, let alone any EphB4 monoclonal antibodies which is capable of promoting apoptosis. Inada et al.

merely use antibodies to EphB4 to isolate arythroid progenitor cells. No therapeutic benefits of these antibodies have been disclosed. The other cited references (e.g., Queen et al. and Stephenson et al.) fail to cure the deficiencies of Inada et al. Absent any evidence that that the EphB4 antibody may have any therapeutic value (e.g., in promoting apoptosis), one of ordinary of skill would not have been motivated to modify Inada's antibodies to make apoptosis-promoting monoclonal antibodies against EphB4 as claimed in the present invention. Even if a skilled artisan would have been motivated to make EphB4 antibodies as therapeutics, there is no reasonable expectation of success in making the claimed apoptosis-promoting antibodies for the reasons as described above.

Further, like Stephenson et al, Inada et al. do not teach, expressly or inherently, an isolated EphB4 antibody which promotes apoptosis in a tumor cell. Therefore, the proposed combination of cited references fails to teach each and every limitation of the claimed invention.

In view of the above, Applicants submit that all of the pending claims are non-obvious over Inada et al. in view of Stephenson et al., and in further view of Queen et al. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants believe that the claims are now in condition for allowance. If an additional fee is due, the Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. **VASG-P01-002**. Please direct any questions arising from this submission to the undersigned at (617) 951-7000.

Dated: August 4, 2008

Respectfully submitted,

By _____

Z. Angela Guo
Registration No.: 54,144
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys for Applicant